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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/042,488	03/16/1998	RONALD M. EVANS	SALK1520-2	5034

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

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37

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/042,488	Applicant(s) EVANS ET AL.	
	Examiner S. Kaushal	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-13,15-24,39,40,47-55 and 57-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-13,15-24,39,40,47-55 and 57-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response filed on 05/30/02 has been acknowledged.

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55 and 57-77 *were pending and were examined in this office action.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF* ***ALL*** *PENDING CLAIMS IS REQUESTED.*

Claim Rejections - 35 USC § 112

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55 and 57-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention** for the same reasons of record as set forth in the office action mailed on 12/20/01.

The applicant argues that in view of the instant specification, one would have no reason to doubt that applicant had possession of the method as claimed. The applicant further argues that claims are not directed to any and all response element but are drawn to response element to which the modified ecdysone receptor binds (response, page 16, para.2-3). The applicant further argues that claims are not directed to any and all modified receptors but are drawn to modified ecdysone receptor (response, page 17, para.3-4). The applicant further argues that a receptor

partner other than a modified ecdysone receptor is optional and the discussion regarding the dimmer partner and dimerization is irrelevant (response, page 18, para.1-2). The applicant further disagrees with office assertion that the steroid/thyroid hormone super family receptors include the members that would expected to have widely divergent functions. The applicant argues that invention should not be limited to the exemplary species provided in the specification (response, page 19, para.1). The applicant concluded that the specification provide adequate written description of all elements required in the invention as claimed.

However, this is not found persuasive because the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). At best the specification as filed discloses modified ecdysone receptor GEcR (containing glucocorticoid response element) and VpEcR (containing Vp16 activation domain) from *Drosophila melanogaster* within the scope of genus comprising the claimed modified receptors (spec. page 6, line 19-33 and fig-1D). The specification further disclosed that Drosophila USP and it mammalian homolog RXR are the only silent partners of insect Ecdysone receptor, which mediates ecdysone hormone responsiveness (spec. page 5, line 33 and fig-1A). In addition the specification disclosed a modified ecdysone receptor VgEcR contain mutation in 3 amino acid residues that render this modified receptor responsive to a hybrid responsive element E/GRE (ecdysone/glucocorticoid response element) see spec. page 6, line 19-33. In addition the specification teaches that the use of modified ecdysone receptor (VgEcR) in combination with hybrid responsive element E/GRE only enable the method as claimed wherein the response element has no binding affinity for FXR receptor (spec. Fig-1B).

The state of the art at the time of filing was such that the ecdysone hormone responsiveness is mediated by the functional ecdysone response complex, a hetrodimer of the insect ecdysone receptor (EcR) either with its natural dimeric partner, the ultraspiracle gene product (USP) or with the retinoid X receptor (RXR) a mammalian homolog of USP (Hoppe et al Mol. Ther. 1(2):159-164, 2000). Similarly, the retinoic acid receptor and the thyroid hormone receptor require dimerization with a second nuclear receptor, the retinoid X receptor. The functional ecdysone receptor is composed of a hetrodimer between the ecdysone-binidng

receptor (EcR) and a RXR homologue, the EcR/RXR complexes repress the transcription in the absence of ligand and recruit coactivators in the presence of the ligand in ecdysone receptor system (Ghbeish et al, PNAS98(7):3867-3872, 2001). However, no mammalian transcription factors have been shown to have a natural enhancer element like the EcRE, which is composed of two inverted half-sites of the sequence AGGTCA spaced by 1 nucleotide and it is difficult to preclude such a possibility (NO et al, PNAS 93:3346-3351, 1996, page 3349, col.1 para.2). The art at the time of filing further teaches that farnesoid X receptor (FXR) can activate certain synthetic promoters containing an EcRE response element in response to farnesoids. The modified ecdysone receptor VgEcR containing mutation in 3 amino acid residues render the modified receptor responsive to a hybrid responsive element called the E/GRE (ecdysone/glucocorticoid response element). Although FXR can activate a promoter containing the wild type EcRE, it cannot activate one containing the E/GRE. Similarly, the E/GRE linked reporter gene is not activated by GR nor does VgEcR activate a dexamethasone responsive promoter (NO et al, page 3349, col.1 para.2).

Although the instant claims have been amended to recite the elements that bind to the modified ecdysone receptor, there is no description of any and all response elements that bind to the modified ecdysone receptor and the respective ligands (as claimed). Furthermore, the specification fails to disclose all modified receptors that mediates the transactivation of an exogenous gene operatively linked to any an all DNA-binding domains or any and all activation domains and has no binding affinity for FXR. There is no description how the structure of Drosophila ecdysone receptor relates to the structure of any naturally occurring ecdysone receptors. In addition, the steroid/thyroid hormone superfamily receptors include members that would expected to have widely divergent functional properties. The specification fails to disclose any modified thyroid hormone receptor system wherein the response element has no binding affinity for FXR and the system modulates the expression of an exogenous gene as claimed. The general knowledge in the art concerning ecdysone receptor does not provide any indication as how the structure of one receptor is representative of other unknown homologs having concordant or discordant functions. The specification only disclosed ecdysteroid induced responsiveness in a modified ecdysone receptor system comprising VpEcR (Drosophila) and E/GRE response element that has substantially no binding affinity for farnesoid-X-receptor. One

cannot describe what one has not conceived. See Fiddes v. Baird, 30 USP2d 1481 at 1483. In Fiddes, claims directed to a mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. In addition, possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention Pfaff v. Wells Electronics, Inc 48 USPQ2d 1641, 1646 (1998). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55 and 57-77 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression of an exogenous gene in an isolated cell containing i) a DNA construct comprising the exogenous gene under the control of the disclosed modified ecydsone response element E/GRE wherein the response element has substantially no binding affinity for farnesoid-X-receptor (FXR), and ii) a modified ecdysone receptor (VgEcR) which in the presence of an exogenous ecdysteroid and in the presence of EcR silent partner (RXR) bind to the response element, does not reasonably provide enablement for the method as claimed wherein an isolated cell comprises a) any and all response elements that has substantially no binding affinity for FXR and b) any and all modified receptors and/or their silent partners containing any and all ligand binding domains, DNA binding domains and activation domains of any and all transcription factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons of record as set forth in the office action mailed on 12/20/01.

The applicant argues that the test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue (response, page 19, para.3). The applicant further argues that the instant specification provides ample guidance to

one skill in the art regarding the ecdysone response element contemplated by invention methods. The applicant further argues that the modified receptor of the present invention requires specific domains as defined in the claims is readily enabled in view of the instant specification (response, page 20, para.2-3). The applicant further argues that claims 72-77 are enabled as the invention only require the modulation of an exogenous gene expression (response, page 21, para.2). The applicant concluded that one skill in the art could readily follow the instant specification to practice the methods to modulate gene expression.

However, this is not found persuasive because applicant's argument alone cannot take place of evidence lacking in the record. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The scope of instant claims encompass a method for modulating the expression of an exogenous gene in an isolated cell comprising a DNA construct comprising the exogenous gene is under the control of any and all response element(s) that binds to modified ecdysone receptor, a modified ecdysone receptor which in the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element. The scope of instant claims also encompass a method for modulating the expression of an exogenous gene in an isolated cell comprising a DNA construct comprising the exogenous gene is under the control of an ecdysone response element, any and all modified receptor(s) which in the presence of a ligand and optionally in the further presence of a receptor capable of acting as any and all silent partner(s) binds to the response element. Furthermore, the scope of instant claims encompass the method as claimed wherein the exogenous gene is a therapeutic gene (see claims 19-21, 64-66). In addition, the scope of the method as claimed encompass the modulation of the expression of an exogenous gene in a mammalian subject (see claims 72-77).

At best the specification teaches modified ecydsone receptor GEcR (containing glucocorticoid response element) and VpEcR (containing Vp16 activation domain) obtained from *Drosophila melanogaster* within the scope of genus comprising the claimed modified receptors (spec. page 6, line 19-33 and fig-1D). The specification further disclosed that Drosophila USP and it mammalian homolog RXR are the silent partner of insect Ecdysone receptor, which mediates ecdysone hormone responsiveness (spec. page 5, line 33 and fig-1A). In addition the specification disclosed a modified ecdysone receptor VgEcR that contain

mutation in 3 amino acid residues which render the modified receptor responsive to a hybrid responsive element E/GRE (ecdysone/glucocorticoid response element) see spec. page 6, line 19-33. In addition the specification teaches that the use of modified ecdysone receptor (VgEcR) in combination with hybrid responsive element E/GRE only enable the method as claimed, wherein the response element has no binding affinity for FXR receptor (Fig-1B).

The state of the art at the time of filing was such that the ecdysone hormone responsiveness is mediated by the functional ecdysone response complex, a hetrodimer of the insect ecdysone receptor (EcR) either with its natural dimeric partner, the ultraspiracle gene product (USP) or with the retinoid X receptor (RXR), a mammalian homolog of USP (Hoppe et al Mol. Ther. 1(2):159-164, 2000). Similarly, the retinoic acid receptor and the thyroid hormone receptor require dimerization with a second nuclear receptor, the retinoid X receptor. The functional ecdysone receptor is composed of a hetrodimer between the ecdysone-binidng receptor (EcR) and a RXR homologue, the EcR/RXR complexes repress the transcription in the absence of ligand and recruit coactivators in the presence of the ligand in ecdysone receptor system (Ghbeish et al, PNAS98(7):3867-3872, 2001). However, no mammalian transcription factors have been shown to have a natural enhancer element like the EcRE, which is composed of two inverted half-sites of the sequence AGGTCA spaced by 1 nucleotide and it is difficult to preclude such a possibility (NO et al, PNAS 93:3346-3351, 1996, page 3349, col.1 para.2). The art at the time of filing teaches that farnesoid X receptor (FXR) can activate certain synthetic promoters containing an EcRE response element in response to farnesoids. The modified ecdysone receptor VgEcR containing mutation in 3 amino acid residues render the modified receptor responsive to a hybrid responsive element called the E/GRE (ecdysone/glucocorticoid response element). Although FXR can activate a promoter containing the wild type EcRE, it cannot activate one containing the E/GRE. Similarly, the E/GRE linked reporter gene is not activated by GR nor does VgEcR activate a dexamethasone responsive promoter (NO et al, page 3349, col.1 para.2). Therefore considering the complexities in the ecdysone responsive systems specification to teach one skill in the art how to make and use the invention commensurate in scope.

Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not

be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

The specification fails to teach any and all response elements to which the modified ecdysone receptor binds and their respective ligands as encompassed by the invention as claimed. Furthermore, the specification fails to disclose any and all modified receptors that mediates the transactivation of an exogenous gene operatively linked to any an all DNA-binding domains or any and all activation domains and has no binding affinity for FXR. The specification fails to disclose any modified thyroid hormone receptor system wherein the response element has no binding affinity for FXR and the system modulates the expression of an exogenous gene as claimed. In addition, the specification fails to disclose the method for modulating the expression of an exogenous gene in isolated cells and/or a mammalian subject comprising a combination of any unrelated modified receptors their silent partners that modulates the expression of an exogenous gene operatively linked to any response element that has no binding affinity to the FXR. The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

The instant specification fails to disclose how one skill in the art would use the invention as claimed without excessive and undue amount of experimentation in view of the state of the art and the limited guidance provided in the specification. To exercise the invention as claimed one would have to characterize and modify any and all receptor that regulates the expression of an exogenous gene operatively linked to any and all response elements containing any and all ligand binding domains, DNA-binding domains and activation domains. The experimentation required would include the identification and modification of thyroid hormone receptors herein the response element has no binding affinity for FXR and the system modulates the expression of an exogenous gene as claimed. In addition the experimentation required would further include the identification of the response elements that has no binding affinity for FXR receptor.

In addition, the invention as claimed encompass a method of modulating the expression of an exogenous gene in a mammalian subject (claims 72-77), which clearly falls in the realm of gene therapy. The earlier office action clearly states that gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations.

The instant invention as claimed requires the delivery of the ecdysone responsive receptor complex into a mammalian subject via viral and non-viral methods, wherein the expression of a therapeutic gene is modulated by the administration of a formulation carrying an ecydsteroid and an activator for the silent partner of the receptor complex. The claimed ecdysone inducible system comprises **RXR and EcR** which hetrodimerize and transactivate the ecdysone response element capable of driving the expression of a gene of interest (specification Fig-2). The instant specification fails to provide guidance regarding how both RXR and EcR constructs are delivered into a single cell in a mammalian subject. The specification fails to provide any guidance to selectively target both constructs into a single cell in order to achieve ecdysteroid induced responsiveness in vivo. At best the specification teaches ecdysone responsiveness in a cell line (293) **in vitro** via transient transfection of a modified ecdysone receptor VgEcR, a hetrodimeric partner (RXR) and an ecdysone inducible reporter gene (example-3), which does not represent the modulation of the expression of an exogenous gene in a mammalian subject.

Furthermore, the specification fails to provide any guidelines for determining which individual need to be administered with the formulation as claimed because an ecdysone inducible therapeutic gene should be in place in the host before the administration of any such formulation. Since, the presence of an ecdysone inducible system in a single cell in a mammalian subject is the prerequisite of instant invention, it is not clear how one skilled in the art would use the invention as claimed without any reasonable expectation of success. Considering the unpredictability in the state of gene therapy art the specification as filed fails to disclose a single working example wherein expression of a wild type and/or therapeutic gene is modulated by transducing "an ecdysone inducible system" into a mammalian subject using a formulation comprising any and all types of ecdysteroids any activator for the silent partner of the receptor complex. In addition, *the modulation of gene expression in vivo by administering to a target cell an ecdysone responsive system (as claimed) is not consider routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.* See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The experimentation required would include the delivery of both RXR and EcR constructs into a single cell in a mammalian subject and subsequent modulation of the transduced ecdysone inducible system using the formulation comprising any and all naturally occurring ecdysones, ecdysone-analog and/or ecdysone mimics.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem Yucel Ph.D. can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
PATENT EXAMINER

Scott D. Priebe
SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER